REVIEW

The globalization of inflammatory bowel disease: the incidence and prevalence of inflammatory bowel disease in Brazil

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Purpose of review
Epidemiological studies of inflammatory bowel disease (IBD) in newly industrialized countries are limited, due to a lack of medical surveillance systems and reliable and unified registries and databases. In Brazil, reliable data on the incidence and prevalence of Crohn's disease and ulcerative colitis is scarce. The objective of the present review is to describe in detail the available data on the incidence and prevalence of Crohn's disease and ulcerative colitis in Brazil.

Recent findings
The authors identified the single four population-based studies which refer to incidence and prevalence of IBD in the country (two from São Paulo, one from Espírito Santo and one from the state of Piauí). These studies demonstrate a remarkable growth in the incidence and estimated prevalence of IBD in Brazil, with higher number of cases in more developed regions.

Summary
The increase in incidence over time and the higher current prevalence are indicative of a historical progression in relation to the number of IBD patients in our country, similar to what was observed in countries from Asia and approximating those of the northern hemisphere. Epidemiological studies with more accurate methodology are needed in Brazil.

Keywords
Brazil, Crohn's disease, epidemiology, inflammatory bowel disease, ulcerative colitis

INTRODUCTION

AQ5 Despite the scarcity of population studies in many developing countries, epidemiological studies related to inflammatory bowel disease (IBD) have shown an increase in both incidence and prevalence of Crohn's disease and ulcerative colitis in different regions of the globe [1]. The evolution of IBD epidemiology in newly industrialized countries in Latin America appears to happen in a similar manner to the one in developed countries of the Western world [2]. Although the incidence is stabilizing in many Western countries, the burden remains high, since the estimated prevalence exceeds 0.3% of the general population in North America and Europe and is as high as 0.7% in Canada in 2018 [3▪▪,4].

Epidemiological studies of IBD in newly industrialized countries are limited, due to a lack of medical surveillance systems and reliable and unified registries and databases, which are the hallmark of many Western countries [5]. Another factor to be considered is the disorganization of health systems in countries of continental dimensions and associated economic problems, such as Brazil, which hinders adequate records, resulting in few population studies to be carried out and published [5].

Healthcare disparities are widened when rural areas are compared with urban areas of the newly industrialized countries [6]. In addition, misdiagnosis of IBD as infectious diseases may be a common occurrence in many regions until there is awareness of the recognition both Crohn's disease and ulcerative colitis as an emerging problem.

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KEY POINTS

- There is scarce reliable epidemiological data regarding incidence and prevalence of IBD in Brazil.

- The single four population-based studies from Brazil show an increase in both incidence and prevalence rates of both Crohn's disease and ulcerative colitis after the turn of the 20th century.

- The number of cases is higher in more developed states of the country, with similar lifestyle as countries from Europe and North America.

- Epidemiological studies with more accurate methodology and registries of patients in different regions of Brazil should be encouraged.

In Brazil, reliable data on the incidence and prevalence of Crohn's disease and ulcerative colitis is scarce because IBD is not a mandatory notifiable disease. Thus, public registries and adequate records of the private healthcare systems are lacking. Currently, few national studies focusing on the epidemiology of IBD in Latin American countries are published. Moreover, the comparison between these studies is complex and imprecise, due to important differences in methodologies used and the periods the studies were carried out [7▪,8].

In view of this scenario, the objective of the present review is to describe in detail the available data on the incidence and prevalence of Crohn's disease and ulcerative colitis in Brazil, discussing possible trends and suggesting future strategies so that better epidemiological studies can be performed.

INCIDENCE OF INFLAMMATORY BOWEL DISEASE IN BRAZIL

Although reports and a series of cases of patients with Crohn's disease and ulcerative colitis have been published in Brazil since the 1960s, it was only after the turn of the 21st century that population-based epidemiological studies with improved methodology were published.

In a population-based study in the same region, Victoria *et al.* [9] retrospectively analyzed 115 patients between 1986 and 2005 evaluating the records of the Hospital of Botucatu University, in São Paulo, with a higher incidence of IBD in urban residents as compared with the rural area. In this study, patients treated outside the referral unit or with mild symptoms were not analyzed, which may have underestimated incidence and prevalence rates. In spite of this, the study shows an increase

in the incidence, more notable in Crohn's disease than in ulcerative colitis. In general, the observed incidence of Crohn's disease was 3.5/100 000 inhabitants and 4.48/100 000 in ulcerative colitis, which summed up to an incidence of IBD in the study period of 9.73/100 000 inhabitants. The incidence of IBD as a whole has changed significantly in the last 5 years of the study interval. Crohn's disease steadily grew over the past 5 years, unlike ulcerative colitis, which showed higher growth at the beginning of the study period, followed by a plateau in later years. Consequently, the ratio of diagnosis of ulcerative colitis to Crohn's disease approximated one.

Parente *et al.* [10], in 2015, analyzed 252 patients with IBD in Piauí state, in the northeast part of the country, between January 2011 and December 2012, with 60.3% of included patients with ulcerative colitis and 39.7% with Crohn's disease. The authors reported a slight increase in IBD cases between 1988 and 1998 at a rate of one to five new patients per year in that decade (exclusively in the public system). In the first decade of the 21st century, a greater increase of annual cases was verified, with the incidence increasing from 0.08 to 1.53 cases/100 000 inhabitants per year during the study period.

Lima Martins *et al.* [11▪], in 2018, carried out a study at the state of Espírito Santo (southeast of the country), which included 1048 patients. This study showed higher numbers than previous reports published in the country. The incidence was calculated based on new cases between the years of 2012 and 2014 (298 patients – 204 with ulcerative colitis and 94 with Crohn's disease). The IBD estimated incidence was of 7.7/100 000 inhabitants/year (5.3/100 000 inhabitants/year for ulcerative colitis and 2.4/100 000 for Crohn's disease). In this study, the incidence of IBD increased from one to eight cases/100 000 inhabitants/year in the study period. The data from this study are more recent and is more representative for including almost all the patients enrolled in the public health system of the region.

Gasparini *et al.* [12▪], in a similar study that captured patients from the public system throughout the state of Sao Paulo, analyzed 22 638 IBD patients between January 2012 and December 2015. The authors described an increase in the incidence of both diseases. The incidence rate of IBD in this state, the most populous and developed in Brazil, averaged 13.30 new cases/100 000 inhabitants/year (Crohn's disease: 6.14/100 000 inhabitants/year and ulcerative colitis: 7.16/100 000 inhabitants/year). This was the highest incidence described in the country to date.

As limitations, these more recently published studies did not include data from the private health system, only analyzing patients who were dispensed

medications within the public system [11[■],12[■]]. Despite this selection bias, these more recent studies show a greater number of new cases than studies conducted in the same region 10 or 15 years ago [9]. Two points may justify these findings. Initially, older data published towards the beginning of the century were underestimated for methodological issues. In addition, there are clear signs of an increase in the incidence of IBD globally, which could be reflected in Brazil in a similar way.

Kotze *et al.* [7[■]], in a systematic review which included all Latin American countries, analyzed 61 articles from several countries from three different databases. Among the Brazilian studies included, when analyzed together, the incidence of IBD seems to have increased steadily over the last generations in Brazil. For example, since the incidence of IBD was originally reported at 0.08 per 100 000 inhabitants in Brazil in 1988, the incidence of Crohn's disease has increased from 0.68 (1991–1995) to 3.5 (2001–2005), reaching a peak from 5.48 per 100 000 in 2015. From 1991–1995 to 2001–2005, the incidence of ulcerative colitis has also increased from 3.86 to 5.3 per 100 000, with a peak of 8.00 per 100 000 in 2015.

Table 1 demonstrates a summary of the incidence rates of IBD in the main population-based studies published until 2018 in Brazil.

PREVALENCE OF INFLAMMATORY BOWEL DISEASE IN BRAZIL

The same aforementioned studies on incidence, also presented interesting data related to prevalence. Victoria *et al.* [9], determined that the estimated prevalence of IBD in 2009 was 22.61 for every 100 000 inhabitants in the region of Botucatu, in the state of São Paulo. In that study, there was a rapid increase in prevalence between 1986 and 2005, with numbers in ulcerative colitis increasing from 0.99 to 14.81/100 000 inhabitants and from 0.24 to 5.65/100 000 in Crohn's disease. The authors argued that although the region has a low

prevalence of IBD, an important increase was noted over the years.

In the study by Parente *et al.* [10], Conducted in the northeastern region of Brazil, with a reduced socioeconomic status, the period prevalence of IBD was 12.8 cases/100 000 inhabitants in 2012. This study did not separate the prevalence between Crohn's disease and ulcerative colitis. Another important limitation is the fact that only patients from the Hospital of the Federal University of Piauí were included in the database (patients of the single local public referral unit in IBD management). Patients treated in other centers of the state were not analyzed, which underestimated the prevalence.

In the study by Lima Martins *et al.* [11[■]], the characteristics of 1048 patients who received medication in the state of Espírito Santo, were analyzed. Considering the state population in 2014 by official agencies [13], the prevalence of IBD was of 38.2/100 000 inhabitants. From them, 935 (63%) were diagnosed with ulcerative colitis (prevalence of 24.1/100 000) and 549 (37%) with Crohn's disease (prevalence of 14.1/100 000), showing a tendency of increase in both diseases in the state.

In the more recent study by Gasparini *et al.*, that analyzed patients who accessed the dispensing of medication by the public health system, the estimated prevalence of IBD in the State of São Paulo from January 2012 to December 2015 was 52.6 cases/100 000 inhabitants (24.3/100 000 for Crohn's disease and 28.3/100 000 inhabitants for ulcerative colitis) [10]. This study, however, is associated with the limitation of missing patients with mild disease off IBD medication or with surgically induced remission and had no medical therapy at the moment of data collection. This could still underestimate results.

According to the aforementioned Latin American systematic review, when analyzing only Brazilian studies altogether, the prevalence of Crohn's disease in Brazil rose from 0.24 (1986–1990) to 24.1 per 100 000 people (2014) [7[■]]. Likewise, the prevalence of ulcerative colitis increased from 0.99

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Table 1. Population studies published in Brazil until 2018 – incidence data

Reference	Period of the study	State	Number of patients included	CD	UC	Nonclassified colitis	IBD incidence overall
Victoria *et al.* [9]	1986–2005	São Paulo	115	3.5	4.48	1.75	9.73
Parente, *et al.* [10]	2011–2012	Piauí	252	–	–	–	1.53
Lima-Martins *et al.* [11[■]]	2012–2014	Espírito Santo	1048	5.3	2.4	–	7.7
Gasparini *et al.* [12[■]]	2012–2015	São Paulo	22 638	6.14	7.16	–	13.30

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

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Table 2. Populational studies published in Brazil until 2018 – estimated prevalence data

Author	Year	State	Number of patients included	CD prevalence	UC prevalence	Nonclassified colitis	IBD prevalence overall
Victoria et al.	2009	São Paulo	115	5.65	14.81	2.14	22.60
Parente et al.	2015	Piauí	252	–	–	–	12.8
Lima-Martins et al.	2018	Espírito Santo	1048	14.1	24.1	–	38.2
Gasparini et al.	2018	São Paulo	22 638	24.3	28.3	–	52.6

CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

to 14.1 over the same period of time. The estimated prevalence of IBD in Brazil was 38.2 per 100 000 in 2014, thanks to the inclusion of the Lima Martins study in the review.

These findings demonstrate the remarkable growth in the estimated prevalence of IBD in our country, and the more recent data position Brazil as a country with an important number of cases, which can be comparable with the more developed regions of the world (IBD intermediate prevalence).

Table 2 shows in detail the estimated prevalence data of IBD in populational studies published in Brazil.

DISCUSSION

Population data related to the epidemiological aspects of IBD in Brazil are scarce. However, besides the few studies published, the increase in incidence over time and the higher current prevalence are indicative of a historical progression in relation to the number of IBD patients in our country, similar to what was observed in countries from Asia and approximating those of the northern hemisphere [2,3■■]. As observed, only four studies present population-based data in the country.

Some factors seem to contribute to the difficulty of obtaining accurate data regarding the epidemiology of IBD in Brazil. Among them, a possible limitation of the professional qualification of the assistant physicians who see these patients is highlighted, as well as difficult access to diagnostic methods used in certain regions of the country. Another possible factor is differential misdiagnoses (mostly with infectious diarrhea or tuberculosis). In addition, a possible delay in diagnosis due to the insidious evolution of IBD and fatal complications without the characterization of the disease recorded as the cause of death may equally contribute to these difficulties [5].

After decades of increasing incidence, the prevalence of IBD is expanding in Brazil. However, important variations in the prevalence of these diseases were observed in different regions of the country. For example, the prevalence of IBD in the State of Piauí (12.8 per 100 000) is significantly lower than in the state of São Paulo (52.6 per 100 000) [10,12■]. Social, economic and cultural development factors possibly influenced these numbers, which are clearly higher in the more developed state of the country (São Paulo) as compared with one of the states with the lowest development index in our country (Piaui) [13]. Nevertheless, in the 25 years of the study period of Parente et al. [10], a gradual increase in the incidence of IBD in the region was still detected, despite the differences already described with more developed areas, classically associated to a greater number of cases of Crohn's disease and ulcerative colitis. This study was conducted in a Brazilian region with the lowest rates of human and socioeconomic development indexes in the country. In line with the low development, the average income per capita of the population of Piauí state (USD 2965.00 per year) is well below the average income per capita from Brazil as a whole (USD 4602.12 per year) [10]. In this Brazilian region, with important economic limitations, IBD is still considered a rare clinical condition as compared with countries with higher development indexes, where incidence rates are historically higher. This example demonstrates the difficulties of having reliable data records in a country with continental dimensions, with different realities depending on the regions and their development status.

The prevalence of IBD in the State of Espírito Santo was among the highest identified (38.2/100 000 inhabitants), in numbers comparable with the Gasparini study from the state of São Paulo [11■,12■]. Both states are located in the southeastern region of the country, an area that is more developed when compared with the states of the north or northeast. These studies have found a trend towards higher rates of prevalence and incidence of IBD in Brazil in recent years as compared with older studies, compatible with regions with moderate incidence and prevalence across the globe. The southeastern region, in addition to being more developed, also presents a population with a similar lifestyle of

developed countries, with a western diet and possible genetic influence, since the population is partially composed of European immigrants and their descendants, factors that could justify the higher incidence and prevalence.

The numbers found in the study by Gasparini *et al.* show similar incidence and prevalence as some European countries, being higher than those found in the systematic review by Ng *et al.* and in older Brazilian studies [2,3■■,9]. These findings demonstrate the theory that the oldest published data possibly underestimated the number of cases of IBD in Brazil, due to methodological and registry limitations. In addition, this study mirrors the findings of the possible acceleration in the incidence of IBD in newly industrialized countries in Asia and Latin America [2].

A large multiethnic country as Brazil, with more than 200 million inhabitants [13], needs more trustable and robust data on the epidemiology of IBD. According to the main studies included in this review, the phenotypic characteristics of both Crohn's disease and ulcerative colitis in Brazil are similar to what is observed in Europe, North America and Asia. However, the country surely is not represented by only these four main population studies. Therefore, studies from other regions such as the south of the country, which has a strong European influence, the mid-west and northern states are also needed to understand the environmental and cultural differences from these areas that can impact the number of IBD cases and compare phenotypes with other regions of the world in more detail.

The lessons learned by reviewing the increasing incidence and prevalence of IBD in Brazil demonstrate that environmental factors may have a crucial role in the context of cause in IBD. As a matter of fact, there are no studies published to date that could explore the possible reasons for the increase of the incidence and prevalence of IBD in Brazil. Factors as the industrial development of the country, as well as the westernization of diet and lifestyle added to internal migration from rural to urban areas could be possible reasons for this increase. Future studies evaluating environmental factors such as smoking, diet, previous infections and microbiome are awaited in the Brazilian IBD population.

An effective epidemiological evaluation is able to guide the development of strategies and the planning of effective actions for better treatment of patients with any disease. Also, these studies help elucidate the cause, providing the opportunity to prevent its onset or unfavorable evolution [14]. The increase in the incidence and prevalence of IBD in Brazil reflects what has been observed for decades in more developed areas, such as Europe and North America. Further epidemiological studies with a more accurate methodology are needed in different states and regions of the country, so that better planning can be carried out, since the increase in the number of cases will reflect in increased costs and use of health resources. Further training of physicians for early diagnosis and appropriate treatment strategies are required, and the role of study groups such as the *Grupo de Estudos de Doenças Inflamatórias Intestinais Brasileiro* will be crucial to achieving these outcomes.

CONCLUSION

Despite the few epidemiological studies published so far in Brazil, there is a clear increase in the incidence and prevalence rates of IBD in our country. Differences among the regions of the country seem to reflect in the number of cases in certain states, with the incidence and prevalence of Crohn's disease and ulcerative colitis being higher in more developed parts of the country. Epidemiological studies with more accurate methodology and registries of patients in different regions should be encouraged for a more accurate description of the epidemiological profile and population trends of IBD in Brazil.

Conflicts of interest

P.G.K. is speaker and consultant for Abbvie, Janssen, Pfizer and Takeda. A.B.Q. and G.G.K. have no disclosures.

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